Autosomal dominant dopa-responsive dystonia: a case report

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INTRODUCTION

Autosomal dominant dopa-responsive dystonia (DRD; OMIM#128230), also known as autosomal dominant Segawa syndrome, is a neurological syndrome caused by heterozygous mutation of the GTP cyclohydrolase I gene (*GCH1*; chr14q22.2). It is characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of oral levodopa. The most common initial symptom is gait difficulties attributable to flexion-inversion of the foot (equinovarus posture). The worldwide incidence is estimated at 1 – 9 cases per 1.000.000 individuals. Despite autosomal dominant inheritance, clinical manifestation is more commonly observed in women (1.3:1 up to 8.3:1), an indicative of sex-biased penetrance.

CASE REPORT

A male patient, currently 10 years old (yo), was referred to the Genetics Outpatient Clinic of Hospital Universitário Júlio Müller (HUJM, Cuiabá-MT, Brazil) for evaluation due to having a sister previously diagnosed with DRD. The patient initially presented adequate neurodevelopment, achieving motor milestones within the expected timeframe. The first motor symptoms appeared at 4 yo, when frequent falls and gait alteration were observed, resembling an equinovarus posture on the right side. No other symptoms were reported. After neurological assessment, pharmacological treatment with 50 mg levodopa/day was initiated and symptoms greatly improved. At 5 yo, the patient was referred to and underwent initial evaluation at our facility. A molecular panel test identified a pathogenic variant at *GCH1* (chr14:54.902.627, GCTTCTCCGCC>GTCA, p.Ala10Hisfs*54). At 7 yo, symptoms of hyperactivity and inattention were noticed at school. At the present time, he is on 200 mg levodopa/day and remains clinically asymptomatic. In contrast, the patient's sister, currently 20 yo, presented the first motor symptoms much earlier, at 1 yo.

Whole exome sequencing identified a *GCH1* pathogenic variant, confirming DRD diagnosis. She is currently under pharmacological treatment and remains asymptomatic. Following identification of *GCH1* pathogenic mutation in both children, molecular testing of the mother was performed. Despite the absence of symptoms, the same *GCH1* mutation was identified in the mother.

DISCUSSION

The patient presents symptoms consistent with the natural history of DRD, as well as a sustained response to low doses of levodopa (maximum benefit is usually achieved with less than 300-400 mg/day of levodopa with a decarboxylase inhibitor). Based on the familial history, which is compatible with DRD in its autosomal dominant form, and identification of a pathogenic *GCH1* mutation of maternal origin, genetic counseling was performed.

CONCLUSION

The patient reported here is a confirmed case of DRD and is being regularly monitored by primary and specialized healthcare professionals in order to manage symptoms and minimize complications.

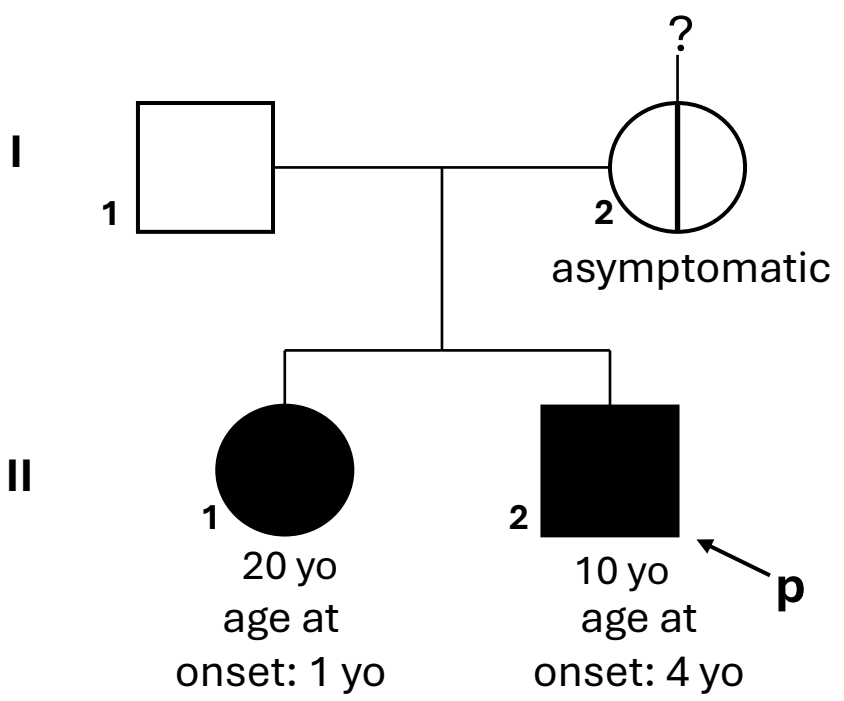

Figure 2: Pedigree of the case reported here.

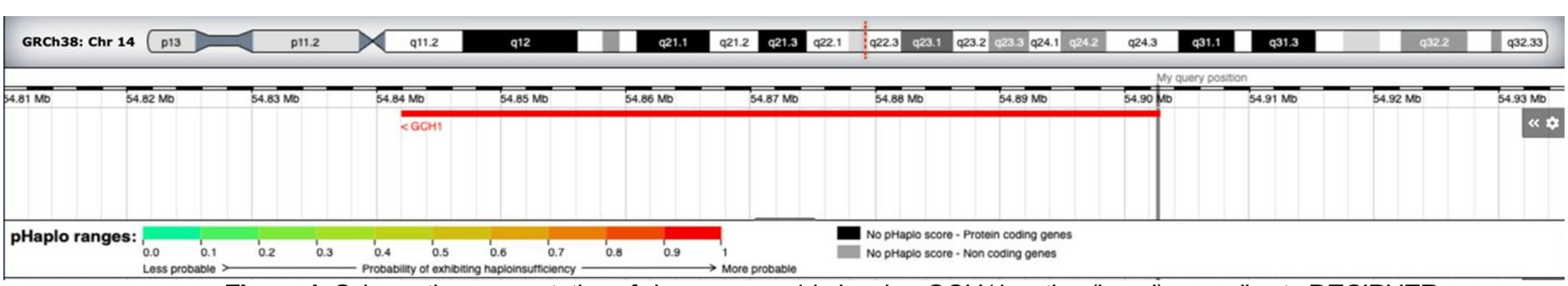

Figure 1: Schematic representation of chromosome 14 showing *GCH1* location (in red) according to DECIPHER.